Listeria monocytogenes: a foodborne pathogen

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Listeriosis, caused by *Listeria monocytogenes*, appears to be increasing in incidence worldwide. The disease is of great concern to the food industry. A recent outbreak in California was linked to the consumption of Mexican-style soft cheese and involved more than 300 cases, 30% of which were fatal. *L. monocytogenes* can be found in a variety of dairy products, leafy vegetables, fish and meat products. It can grow in refrigerated foods and is more heat resistant than most vegetative microbes. The epidemiologic features of listeriosis are poorly understood, and the minimum infectious dose is unknown. Those predisposed to listeriosis include immunocompromised people and pregnant women and their fetuses. Meningitis, spontaneous abortion and septicemia are the primary manifestations of the disease. Early recognition is critical for successful treatment, and ampicillin is the preferred drug. Listeriosis should be considered in any febrile patient with neurologic symptoms of unknown origin, as well as in women with unexplained recurrent miscarriages, premature labour or fetal death. A food source should be the prime suspect if any isolated case or outbreak occurs.

La fréquence des infections à *Listeria monocytogenes* est en augmentation apparente dans le monde entier et inquiète fort l'industrie alimentaire. Une épidémie récente en Californie, de plus de 300 cas dont 30% mortels, était reliée à l'ingestion d'un fromage à pâte molle de type mexicain. Ce microbe se trouve dans nombre de produits laitiers, de légumes dont on consomme les feuilles, de poissons et de viandes. Il peut se multiplier sous réfrigération et se montre plus résistant à la chaleur que la plupart des microbes végétatifs. Les caractéristiques épidémiologiques des listérioses sont mal comprises; la dose infectieuse minimale n'a pas été déterminée. Sont prédisposés à la listériose les sujets immunocompromis et les gestantes et leurs foetus. Elle se manifeste surtout par des méningites, des fausses-couches et des septicémies. Le diagnostic précoce est de première importance pour le succès du traitement, qui se fait de préférence par l'ampicilline. Il faut penser à une listériose devant tout malade fiévreux qui présente des symptômes neurologiques de cause inconnue et chez toute femme accusant des fausses-couches, des naissances prématurées ou des morts-nés à répétition et inexpliqués. Que le cas soit isolé ou qu'il s'agisse d'une épidémie, il faut chercher surtout du côté d'une contamination alimentaire.

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At least four outbreaks of listeriosis have been associated with food within the last 7 years.[1-4] *Listeria monocytogenes*, first identified in 1926, by Murray and associates,[5] has suddenly emerged as a significant pathogen that can be found in a variety of foods. These outbreaks and the recorded incidence rates among humans probably represent only a small proportion of the actual cases. This review should stimulate attempts in Canada to link the diagnosed cases of listeriosis with the consumption of specific contaminated foods.

Historical review

The first confirmed case of *L. monocytogenes* infection in Canada was reported in 1951 in a pregnant woman who had been in the country for 1 year after emigrating from Russia.[6,7] Since then reported cases in Canada have been sporadic except for an outbreak of 41 cases in Nova Scotia

in 1981.[4] A total of 381 cases have now been documented in Canada (Laboratory Centre for Disease Control [LCDC], Department of National Health and Welfare, Ottawa: unpublished data).[6-8] Infections are reported throughout the year but occur more frequently in the summer. Some reports have suggested an increased incidence rate among people who are immunocompromised,[8] but the findings have been inconclusive.

Except for the outbreak in Nova Scotia, which involved contaminated raw cabbage, food consumption has not been implicated as a possible mode of transmission in Canada. Given the ubiquitous nature of the organism, environmental or occupational exposure is usually the source of infection. Between 1971 and 1984, 28 deaths were attributed to listeriosis, 7 being reported in 1984 (LCDC: unpublished data). There was a slight increase in the number of cases between 1982 and 1984, but this may have been due to the Nova Scotia outbreak and not a real increase in incidence. Data on the population at risk are unavailable; therefore, risk-specific attack rates cannot yet be calculated.

The studies of Schlech and colleagues[4] have suggested that *L. monocytogenes* is carried by 5% of the general population. Fecal carriage has been reported in 29% of poultry workers and in 77% of public health laboratory workers involved in *L. monocytogenes* isolation.[9] The public health importance of human fecal carriage is not known.

Biologic features

L. monocytogenes is a gram-positive, microaerophilic, asporogenic bacillus that has a characteristic tumbling motility between 20°C and 25°C and that produces slight β-hemolysis on sheep-blood agar. It can grow at a variety of temperatures, from 1°C to 45°C,[10] and thus can thrive in foods kept at refrigeration temperatures.

In the laboratory *Listeria* can frequently be missed or misidentified.[11,12] One must be careful not to overlook *Listeria* as a contaminating organism, especially when symptoms and conditions suggest listeriosis. The characteristics that distinguish *Listeria* from other morphologically similar organisms are listed in Table I.

There are 16 recognized serotypes,[10,13] given that there are at least 15 different "O" (or somatic) antigens and 5 "H" (or flagellar) antigens. Serotypes 1/2a, 1/2b and 4b account for more than 90% of the cases reported worldwide.[14]

A phage-typing system has helped in the epidemiologic investigations of foodborne outbreaks of listeriosis. The major system now used allows identification of 54% of the serogroup 1/2 strains and 77% of the serogroup 4 strains of *L. monocytogenes*.[15] However, a recent report has suggested that the phage type of a given *Listeria* strain can change with time.[16] Thus, the current phage-typing system must be modified, or an alternative to phage-typing must be developed. Several researchers at the Centers for Disease Control (CDC), Atlanta, are investigating a method that involves isoenzymes to differentiate the strains.

Source

L. monocytogenes can be isolated from a variety of sources: poor-quality silage, vegetation, soil, sewage, stream water, mud, slaughter-house waste, milk of normal and mastitic cows, and feces of healthy humans. In addition, the organism has been isolated from at least 37 species of mammals and 17 species of fowl, flies, ticks, fish and crustaceans.[10,14]

Pathogenicity

The tests for pathogenicity include the ability to cause keratoconjunctivitis in guinea pigs (Anton's test), toxicity in chick embryos and death in mice.[17]

Virulence factors

Many potential virulence factors have been identified in the literature; these may or may not be important to the overall pathogenicity of *L. monocytogenes*.[18] The more important factors appear to be a monocytosis-producing agent,[5,19] a lipopolysaccharide-like material,[20-23] hemoly-

Table I — Characteristics of *Listeria monocytogenes* and morphologically similar microorganisms

Organism	Characteristic					
	Morphologic features	Motility (at 22°C)	Hemolysis	Catalase production	Salicin fermentation	Trehalose fermentation
L. monocytogenes	Coccoid, rods	+	β	+	+	+
Erysipelothrix rhusiopathiae	Slender rods	−	α	−	−	−
Lactobacillus	Rods	−	α	−	+/−	+/−
Corynebacterium	Rods	−	+/−	+/−	−	+/−
Kurthia	Pleomorphic, filamentous	+	−	+	−	−
Streptococcus	Cocci	−	+/−	−	+	+/−

sin(s)[24-26] and oxygen species such as hydrogen peroxide and superoxide.[27,28]

Heat resistance

An early study by Bearns and Girard[29] showed that *L. monocytogenes* may be able to survive pasteurization if present in fresh milk at concentrations of more than 5×10^4 organisms/ml. More recent studies have shown that the organism can survive the heat associated with the spray-drying of skim milk and the manufacturing of cottage cheese.[30,31] Conversely, Bradshaw and collaborators[32] and one of us (J.M.F.: unpublished data, 1987) found that *L. monocytogenes* could not withstand pasteurizing temperatures.

The organism may be able to survive pasteurization because it resides within leukocytes, which apparently provide some form of protection. To test this hypothesis, the milk from cows inoculated with *Listeria* was subjected to pasteurizing temperatures;[33] *Listeria* was found to survive pasteurization in some instances, but how closely the experiments resembled natural conditions is unknown. Studies of the milk from cows that are naturally infected with *L. monocytogenes* are under way at the Health Protection Branch.

Outbreaks of foodborne infection

A large outbreak in Halle, East Germany, between 1949 and 1957 was linked to the consumption of unpasteurized milk (sour milk, creams and cottage cheese were also considered possible sources);[34] this appears to be one of the first documented reports of listeriosis linked to food consumption.

From 1979 to 1985 four food-associated outbreaks were reported in North America (Table II). Of the 23 patients described by Ho and coworkers[3] 5 died; however, only 2 died from listeriosis. Interestingly, the use of antacids was found to be a risk factor for listeriosis; the neutralization of gastric acids may play an important role in the initial survival of the organism after ingestion.

The cabbage responsible for the outbreak in the Maritimes in 1981[4] had been grown in fields fertilized with compost and raw manure from a flock of sheep known to have had listeriosis.

Table II — Documented outbreaks of listeriosis associated with food in North America

Location, year	Food	No. of cases (and deaths)
Boston, 1979[3]	Lettuce, celery tomatoes	23 (5)
Nova Scotia, 1981[4]	Coleslaw	41 (18)
Massachusetts, 1983[2]	Pasteurized milk	49 (14)
California, 1985[1]	Mexican-style soft cheese	314 (105)

In the outbreak linked to pasteurized milk in Massachusetts in 1983[2] the milk in the bulk tank of one of the farms supplying the incriminated processing plant contained *L. monocytogenes* serotype 4b, which was also identified in 32 of the 40 isolates from cases.

In the spring of 1985 there was a large outbreak of listeriosis centred in California that was linked to the consumption of a Mexican-style soft cheese produced by a company in California.[1] Investigation of the manufacturing plant revealed that some of the raw milk might not have been pasteurized. It was extremely fortunate that most of the cases involved mothers and their infants who presented to the same hospital; otherwise, the outbreak might have been missed.

All four of the food-related outbreaks in North America were caused by *L. monocytogenes* serotype 4b; this serotype may therefore be more pathogenic than the others.[3]

Food surveys

The California outbreak in 1985 prompted surveys of various cheeses sold in the United States and Canada. *L. monocytogenes* was detected in soft and semisoft cheeses from two manufacturers in the United States, one manufacturer in Canada and four plants in France.[35,36] In addition, recent surveys of dairy products in the United States have resulted in recalls of certain ice creams, sherbets, chocolate milk and ice-milk products.[37,38] The Health Protection Branch failed to identify any contaminated cheese produced in Canada; however, two brands of semisoft cheese from France were found to be contamined with *L. monocytogenes* (J.M.F.: unpublished data, 1986).

Listeria has now been found in raw and possibly pasteurized milk,[2,39] cheeses,[35,36] ice cream, sherbet, chocolate milk and ice-milk products,[37,38] leafy vegetables,[3,4] fish,[14] raw meats and chicken,[18] and fermented sausage.[40]

Listeriosis in humans

People predisposed to *Listeria* infection include pregnant women and their fetuses, newborns, recipients of immunosuppressive or corticosteroid therapy, those with underlying diseases such as cancer, hepatitis and alcoholism, and those undergoing long-term hemodialysis.[41] Neonatal listeriosis accounts for the largest recognized group of infections due to *L. monocytogenes*.[42]

The primary manifestations of listeriosis include meningitis, spontaneous abortion and septicemia. Peritonitis, local abscess formation, endocarditis, urethritis, endophthalmitis, conjunctivitis, hepatitis, arthritis and cutaneous lesions have also been reported.[14,41,43,44]

Pregnant women with listeriosis present with a mild illness that resembles influenza. The fetus is

usually aborted spontaneously if it is infected during the first trimester; if infection occurs later in the pregnancy the fetus may be stillborn or the newborn baby acutely ill. In neonatal listeriosis two distinct clinical syndromes are usually present. An early-onset syndrome, which is primarily septicemic, is associated with low birthweight, and is characterized by increased neonatal mortality rates (30%) and a higher frequency of reported obstetric complications. The late-onset or meningitic form of the disease occurs in infants of normal birthweight and is characterized by a low death rate (10%) and no obstetric complications.[42]

CDC has now classified listeriosis as a reportable disease; LCDC is trying to follow suit. Available data indicate that *L. monocytogenes* is infrequently identified as a human pathogen. Most infections are probably asymptomatic and develop in vaginal, cervical or intestinal tissues.[6] The incidence rate is increasing worldwide,[18,41,45] possibly because of the increased awareness of the disease, the frequency of organ transplantation, the increasing number of cancer patients and the increasing size of the elderly population.

Although there is no general agreement on the best therapy for listeriosis, ampicillin, with or without an aminoglycoside, is still recommended.[46] Trimethoprim–sulfamethoxazole was found to be effective in controlling meningitis due to *L. monocytogenes*.[47]

Immune response

Protection against listeriosis clearly seems to rely on cellular rather than humoral immunity.[48] In mice resistance against infection is regulated genetically and can be divided into three phases.[49] The first phase depends on the presence of fixed or resident macrophages in the tissue. Studies have shown that the macrophages will destroy about 90% of the organisms that are present initially; the remaining bacteria grow logarithmically within susceptible macrophages in the liver and the spleen, maximal numbers being reached 48 to 72 hours after the initial exposure.[50]

The second phase of resistance in mice involves the accumulation of monocyte-derived inflammatory macrophages. There is a prompt influx of these cells, which are able to control the rapid bacterial growth. Susceptible mice have a shortage of these macrophages at the site of infection. The inflammatory response seems to be triggered by the listerial resistance gene.[51]

The third phase of resistance results in the elimination of the organism and depends on the accumulation of immunologically activated macrophages.[52,53]

Serologic tests

Although a number of tests have been described for the serologic diagnosis of listeriosis, the agglutination assay remains the standard method of detecting antibodies to *L. monocytogenes*.[54–56]

The use of serologic tests for diagnosing *Listeria* infections seems to be of limited value, however. Newborns and immunocompromised people may not show an increased antibody titre. *L. monocytogenes* antigens will cross-react with the antigens of other gram-positive bacteria[57,58] (most notably *Staphylococcus aureus* and *Streptococcus faecalis*); therefore, even patients with no previous exposure to *Listeria* may have a substantial *Listeria* agglutination titre. There appears to be no change in the antibody production from IgG to IgM during the course of infection; therefore, IgM cannot be used as an indicator of recent infection.[56]

Detection of *Listeria* in foods

There is no acceptable method being used to isolate *Listeria* from foods, although several promising new methods have been described.[39,59–62] The cold enrichment procedure,[63] in which samples are kept at 4°C and subcultured weekly for up to 6 months, still appears to be the most sensitive method. However, a more rapid and sensitive test must be developed to detect *Listeria* in foods.

Surveillance in Canada

Listeriosis is a notifiable disease in only two provinces, neither of which has to report the cases to LCDC. However, contact between federal and provincial laboratories is constant, so that recording of confirmed cases is probably good. Less severe illness possibly goes undiagnosed, and early termination of pregnancy without fetal sepsis, or unsuspected cases ending in stillbirth, do occur. The difficulty in identification and the lack of specificity of the serologic tests have resulted in an incomplete epidemiologic picture of listeriosis in Canada.

A surveillance program for *L. monocytogenes* infection in Canada is being planned by the Department of National Health and Welfare to determine the public health importance of food contamination. A specific objective is to identify infected patients and their surrounding controls by variables that may lead to an elaboration of important links between infection and specific foods. A reference laboratory will be established to assist with identification of the organism and with subtyping (serotyping, phage typing and isoenzyme typing) for epidemiologic purposes.

Overview

Even though the source of most *Listeria* infections is unknown, the evidence of foodborne transmission in humans is now quite convincing.

The organisms' chances of survival increase if the gastric acidity is reduced because of antacids or if the food provides some protection against the gastric acid.[3,64] Once in the intestine the bacteria possibly are taken up by M cells (membranous epithelial cells) and transported to the underlying lymphoid tissue, where they are destroyed by monocytes.[65,66] The ability of an organism to be transported by M cells has been considered to be a positive virulence factor, as it allows easy entry into the body.[67]

Only a few people actually acquire listeriosis; in healthy people the infection is apparently controlled by activated macrophages, but occasionally illness develops.

Because of the lack of information on the rate of contamination of foods and on the risk of invasive disease among susceptible people exposed to the organism, it is difficult to recommend the avoidance of particular foods by high-risk groups. However, the often fatal consequences in these groups, the ability of *L. monocytogenes* to grow in refrigerated foods and the possible survival of organisms in some heat-treated products should be of serious concern to health professionals.

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Meetings

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Sept. 14-16, 1988

21st Annual Conference of the Human Factors Association of Canada
Four Seasons Hotel, Edmonton
Dr. Shrawan Kumar, conference chairman, Department of Physical Therapy, University of Alberta, Edmonton, Alta. T6G 2G4

October

Oct. 2, 1988

3rd Annual Conference on Physician Manpower
Hôtel Meridien, Montreal
Abstract deadline is May 13, 1988
Eva Ryten, Association of Canadian Medical Colleges, 1006-151 Slater St., Ottawa, Ont. K1P 5N1; (613) 237-0070

Oct. 3-4, 1988

Annual Meeting of the Association of Canadian Medical Colleges and the Association of Canadian Teaching Hospitals
Hôtel Meridien, Montreal
Janet Watt-Lafleur, executive secretary, Association of Canadian Medical Colleges, 1006-151 Slater St., Ottawa, Ont. K1P 5N1; (613) 237-0070

Oct. 16-17, 1988

15th Annual Meeting of the Canadian Sex Research Forum
Glenerin Inn, Mississauga, Ont.
Abstract deadline is May 31, 1988
Dr. R.W.D. Stevenson, executive director, Canadian Sex Research Forum, Sexual Medicine Unit, Shaughnessy Hospital, 4500 Oak St., Vancouver, BC V6H 3N1; (604) 875-2027

Oct. 24-26, 1988

Physician Manager Institute 1988: Leadership Skills Development
Prince of Wales Hotel, Niagara-on-the-Lake, Ont.
Chuck Shields, Canadian College of Health Service Executives, 201-17 York St., Ottawa, Ont. K1N 5S7, (613) 235-7218; or Alexandra Harrison, Canadian Medical Association, PO Box 8650, Ottawa, Ont. K1G 0G8, (613) 731-9331

November

Nov. 13-20, 1988

Toronto Stroke Workshop in Jerusalem
This meeting has been rescheduled for Sept. 14-16, 1988 in Toronto. See September items for details.